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Host–guest inclusion complex of β-cyclodextrin and benzoic acid in water–ethanol solvents: spectroscopic and thermodynamic characterization of complex formation

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Abstract

In this study, an inclusion complex of benzoic acid with *β*-cyclodextrin (BA-*β*CD) was obtained from water–ethanol solvents. The yield of complex synthesis in binary mixtures is greater than in water and reaches maximum value at 0.10 mol fraction of ethanol. Results of FTIR spectroscopy analysis showed that the main difference in the spectra of the acid and inclusion complex was observed in the frequency ranging from 2500 to 3100 cm^{-1}, corresponding to aromatic hydrogen vibrations. These vibrations are highly attenuated in complex. Phase solubility and differential scanning calorimetry studies revealed that the inclusion complex was obtained with 1:1 stoichiometric ratio and the solubility of benzoic acid increased with an increase in β-cyclodextrin concentrations in water. The logarithm of stability constant in water was found to be $\lg K = 1.99$. The thermodynamic parameters for the reaction of (BA-*β*CD) complex formation in H_2O–EtOH solvents were determined from calorimetric experiments carried out by means of the calorimetric titration system TAM III (TA Instruments) at $T = 25$ °C. The heat effects of mixing β-cyclodextrin solutions with benzoic acid were obtained from water–ethanol mixed solvents containing $X(\mathrm{EtOH}) = (0.00, 0.10, 0.20$ and $0.30)$ mole fraction at pH = 3.6 and $T = 25$ °C. However, at $X(\mathrm{EtOH}) = 0.30$ mol fraction, according to the calorimetric titration data, no complex formation occurs. When transferring from H_2O to H_2O–EtOH solvents, complex stability decreases from $\lg K = 2.4$ to $\lg K = 0.7$, wherein the reaction exothermicity increases from − 12.2 kJ mol^{-1} to − 44.3 kJ mol^{-1}. An increase in the exothermicity of complexation is accompanied by a decrease in the entropic contribution to the change in the reaction Gibbs energy.

Keywords Benzoic acid · Complex formation · Enthalpy · Gibbs energy · Mixed solvent · β-cyclodextrin

Introduction

Benzoic acid (BA) is the simplest aromatic carboxylic acid that inhibits the growth of mold, yeast and some bacteria. Thus, BA and its salts are usually used as food preservatives, beverages and cosmetics. However, the high doses of BA can affect the liver and kidneys and irritate skin and eyes [1, 2]. It has been shown that BA can combine with ascorbic acid to obtain benzene that is highly dangerous for living organisms [2]. However, the solubility of BA in water is poor, which significantly decreases its bioavailability. Currently, there are several methods to improve solubility of poorly soluble drugs, which include pH adjustment, micronization, solid dispersion [3], cosolvent addition [4], and surfactant addition [5]. One of the simplest and most effective ways is encapsulation of cyclodextrins. β-cyclodextrin (βCD) is composed of seven glucopyranose units forming a

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cyclic, cone-shaped cavity with a hydrophilic outer surface and a relatively hydrophobic inner surface [6]. The ability of cyclodextrins to form inclusion complexes with a guest molecule depends on two main factors. The first critical factor is the compatibility of the size of the guest molecule with the diameter of host cavity. If the guest has the wrong size, it will not fit properly into the cyclodextrins cavity. The second critical factor is the thermodynamics of complexation between reagents, products of reaction and solvents [7, 8]. For a complex to form, there must be a favorable net energetic driving force that pulls the guest into the cyclodextrins [9].

In addition, water also forms stable hydrates with cyclodextrins, complicating the complexation. Most studies of intermolecular interactions focused on the study of selective recognition processes in aqueous solutions. The molecular complexation of cyclodextrins with aromatic carboxylic acids compounds in water is usually characterized by low stability of complexes and low exothermicity of complexation, making it difficult to obtain molecular complexes, their study and further practical use. Previous studies indicated that adding a small amount of cosolvent to water facilitates the complexation of βCD with hydrophobic guest [10]. Recently, cosolvents have been widely used in the synthesis of organic substances and they seem to be promising factors for creating supramolecular pharmacologically active structures. They work by reducing the hydrogen bond density of water and consequently its ability to "squeeze out" nonpolar solutes [11]. A combination of both cosolvent and cyclodextrin additions has a particular interest. Some authors observed synergistic effects of cosolvency and complexation [12, 13]. For example, in the water-organic solvents, the complexation constants of pyrene/cyclodextrins were found to be greater than in water [12]. The authors suggested that the organic solvents play the role of a space-regulating molecule and therefore the drug molecule can better fit into the cavity of cyclodextrin. However, in other studies, it was found that the antagonistic effect of cosolvents decreases the complexation constant when compared with that in water [14, 15].

Some studies on the interaction between BA and βCD have already been reported [1, 2, 16, 17]. It has been demonstrated that BA forms 1:1 inclusion complex with βCD in water as follows:

$$\mathrm{BA} + \beta\mathrm{CD} \leftrightarrow \mathrm{BA}\text{-}\beta\mathrm{CD} \quad (1)$$

No literature data about the complexation between BA and βCD in H_2O–EtOH mixed solvent were found. Therefore, it is necessary to consider the influence of water–ethanol solvent compositions on the complexation process of BA with βCD, and its thermodynamics in water–ethanol solvents. In addition, we reported the effects of cosolvency and complexation in this case and analyzed the solvation-thermodynamic contributions of reagents to the change in the thermodynamic characteristics of complex formation.

Materials and methods

Materials

BA was purchased from Sigma-Aldrich and βCD from Fluka, and both reagents were used as received without further purification. The water content in βCD was determined by thermogravimetry and considered during calculation of the concentration. Thus, βCD contained 7.5 mass% of water. Ethanol of Xilong Scientific Co. (China) was distilled under atmospheric pressure. The residual water was determined densimetrically to be 1.81 mass%. Dimethyl sulfoxide of Xilong Scientific Co. (China) was used as received without further purification. All experiments were carried out in distilled water.

Preparation of inclusion complex

A solid-state complex between BA and βCD in 1:1 molar ratio was prepared. BA (0.41 g, 3.33 10^{-3} mol) and βCD (3.78 g, 3.33 10^{-3} mol) were accurately weighed and dissolved in 100 and 300 cm^3 water–ethanol solvents, respectively, and composition of ethanol in mixture solvent is 0.00; 0.05; 0.10; 0.20; and 0.24 mol fraction. The solution of βCD was added into the BA solution, 10 cm^3 each time, and was stirred by a magnetic stirrer for 24 h at 25 °C. The reaction solution was settled for 48 h at 4 °C to obtain a fine white precipitate. The precipitate was washed several times with dimethyl sulfoxide (DMSO) and dried in vacuum oven.

The complexation yield was calculated as the ratio of the dried complex mass to the sum of BA and βCD:

$$Y = \frac{m(\mathrm{BA}\text{-}\beta\mathrm{CD})}{m(\mathrm{BA}) + m(\beta\mathrm{CD})} \times 100\% \quad (2)$$

where m(BA-βCD), m(BA) and m(βCD) are the masses of the obtained complex, BA and βCD, respectively.

Methods

Fourier transforms infrared (FTIR) spectroscopy

Fourier transform IR spectra were recorded on a Nicolet iS10 (Thermo Scientific-USA) spectrophotometer. The spectra for BA, βCD and their complexes were recorded. Samples were prepared in KBr disks with a hydrostatic press

at a force of 5.2 T cm^{-2} for 3 min. The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential scanning calorimetry (DSC)

BA, βCD and inclusion complex (BA-*β*CD) were studied by a differential scanning calorimeter (DSC; DSC204F1 (NETZSCH-Germany). Accurately weighed solid samples (approximately 3–4 mg) were placed in aluminum pans and scanned from 25 to 300 °C at a constant heating rate of 10 °C min^{-1}, under the air atmosphere. The temperature for the onset of melting (T_{onset}) was obtained from curves by taking the slope of the melting curve at the inflection point and extrapolating to the baseline.

The differential scanning calorimeter was preliminarily calibrated with a pure indium standard. Obtained values T_{onset} for indium ($T_{onset} = 155.8 \pm 0.03$ °C) and heat of fusion ($H_f = 28.20 \pm 0.20$ J g^{-1}) are in agreement with values recommended in [18, 19].

Phase solubility diagrams

The phase solubility diagram was obtained according to the Higuchi and Connors method [20]. An excess amount of BA was added to 25 cm^3 of deionized water containing increasing amounts of βCD, and the initial concentration of βCD is changed in the range of $0 \div 7$ mM. The corresponding thermodynamic equilibrium conditions were reached by shaking the tubes for 72 h at 25 ± 1 °C. UV–Vis spectrophotometer (S80, Biochrom, UK) was used to determine concentrations of the dissolved BA at 273 nm. Samples were filtered through a membrane with a 0.45 μm pore diameter. The binding stability constant (K_s) of the complex was calculated from the phase solubility diagram according to Eq. (3):

$$K_s = \frac{\text{slope}}{S_o(1 - \text{slope})} \quad (3)$$

where S_o is the solubility of BA at 25 °C in the absence of βCD and slope means the corresponding slope of the phase solubility diagrams, i.e., the slope of the BA molar concentration versus βCD molar concentration graph.

Isothermal titration calorimetry (ITC)

The thermodynamic parameters for the reaction between BA and βCD in water–ethanol solvents were obtained from the calorimetric experiments carried out by means of the TAM III (TA Instruments, USA) calorimetric titration system at a temperature of 25 °C, equipped with a 20 cm^3 titration cell. The microcalorimeter was electrically calibrated, and the calibration was verified with a binding reaction between Ba^{2+} and 18-crown-6 in water at $T = 25$ °C [21]. Obtained values ($\lg K = 3.24 \pm 0.40$ and $\Delta_r H = -(30.9 \pm 0.8)$ kJ mol^{-1}) correspond with values recommended in [19].

The application of the traditional calorimetric titration with sequential addition of a number(s) of injections into a calorimetric cell is limited by low solubility of BA in H_2O–EtOH mixtures. This prevented us from obtaining the necessary concentration ratio of the reagents during one titration experiment. A single addition of titrant portions into a cell solution in each calorimetric titration experiment allows the creation of the optimum concentration conditions for such systems. This experimental procedure was successfully adopted earlier by us for a calorimetric investigation of a "host–guest" complex formation of 18-crown-6 and cryptand [2.2.2] with some amino acids and peptides, as well as for complexes of Cu(II) with glycyl-glycyl-glycine [22–25]. In a typical calorimetric experiment, the initial concentrations of BA and βCD were changed in the range of $1.4 \times 10^{-3} \div 5.92 \times 10^{-1}$ mol dm^{-3} and $1.8 \times 10^{-2} \div 2.65 \times 10^{-2}$ mol dm^{-3}, respectively. Calorimetric measurements were carried out in water–ethanol solvents containing 0.00, 0.10, 0.20 and 0.30 mol fraction of EtOH. The primary experimental values of solute and solvent mass have been used. Solutions were freshly prepared just before the measurements in a phosphate buffer, at pH = 3.6, which correspond to the pH of BA solutions with concentrations used in experiments. The range of concentrations of used water–ethanol mixtures is restricted by the low solubility of βCD in water–ethanol mixtures, [26, 27], which limits the set of BA: βCD concentration ratios were required for simultaneous calculation of the stability constants of BA-*β*CD complex and the enthalpy of its formation reaction from the calorimetric data. However, at $X(\text{EtOH}) = 0.30$ mol fraction, according to the calorimetric titration data, no complex formation occurs. The example of primary experimental data is given in Table 1.

The fraction distribution diagrams of particles in water–ethanol solutions containing BA are calculated by the software KEV [28]. The results show that in water at pH 3.6, the molecular and anion forms of BA are 79.81% and 20.19%, respectively. In water–ethanol solvents at pH 3.6, the molecular form was predominated (94.06% and 98.66% at 0.10 and 0.20 mol fraction of ethanol, respectively. The acid–base equilibrium constants of BA in water–ethanol solvents were from the literature [29] and were used at KEV mathematic treatment. The examples of the fraction distribution diagrams of particles of BA are observed in Fig. 1. Thus, it can be confirmed that the obtained thermodynamic parameters of complex formation in water–ethanol solvents are referred to as the association between molecular forms of BA and βCD.

Table 1 Example of primary experimental data for the calorimetric experiments of mixing of βCD with BA in H_2O–EtOH solvent at $X_{EtOH} = 0.20$ mol fraction, and $T = 298.15$ K. Phosphate buffer, pH = 3.6

C^a(BA)/mol dm^{-3}	C^a(βCD)/mol dm^{-3}	C^b(BA)/mol dm^{-3}	C^b(βCD)/mol dm^{-3}	Q_{compl}/mJ	$-Q_{dil}$/mJ
βCD in cell and BA in syringe					
0.592	0.0144	0.0078	0.0142	375.2	249.7
0.592	0.0144	0.0078	0.0142	369.7	249.7
0.592	0.0058	0.0078	0.0057	165.1	249.7
0.592	0.0058	0.0078	0.0057	151.8	249.7
0.592	0.0058	0.0116	0.0057	155.9	258.0
0.592	0.0058	0.0116	0.0057	138.8	258.0
BA in cell and βCD in syringe					
0.050	0.0180	0.0493	0.0002	23.1	− 12.0
0.030	0.0180	0.0301	0.0002	18.7	− 12.0
0.136	0.0180	0.1340	0.0002	14.0	− 12.0
0.0118	0.0180	0.0180	0.0002	8.9	− 12.0

C^a is the initial concentration of reagents; C^b is the analytical concentration of reagents in cell; Q_{compl} is the heat effect of complexation between BA and βCD; and Q_{dil} is the heat effect of dilution of βCD or BA solution in a suitable solvent

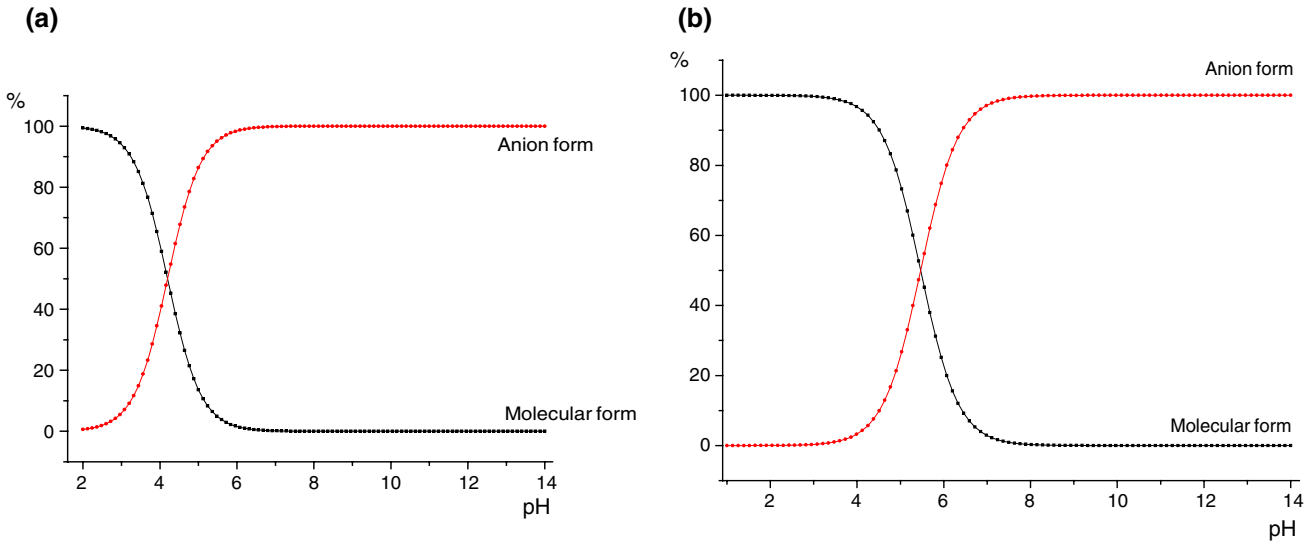

Fig. 1 Fraction distribution diagrams of particles of benzoic acid in water (**a**) and in water–ethanol solvents with concentration of ethanol of 0.2 mol.fr. (**b**) at pH 3.6

Results and discussion

Determination of yield of complexation

Complex formation between BA and βCD depends on the composition of binary solvents. Complex was obtained in water–ethanol solvents with different concentrations of ethanol ($X_{EtOH} = 0.00$, 0.10, 0.20 and 0.24 mol fraction). Yield of complexation (Y) is shown in Table 2.

As reported in Table 2, the yield of the obtained complex in binary media was greater than in pure water. There are some differences in the complexation between BA and βCD in water: The part of the interior of the βCD cavity in which BA molecule is located can be more hydrophobic than in the presence of EtOH in solvent, and this can be the reason for the higher yield of complexation in binary solvents. In order to clarify this result, we took into account the difference in the structure of the pure

Table 2 Complexation yield (Y) at different compositions of solvents (X_{EtOH})

X_{EtOH} molar fraction	0	0.05	0.10	0.20	0.24
Yield (Y)/% ± 0.6	63.0	72.2	88.3	79.8	77.2

solvents as well as in the thermodynamic properties of the solvent mixtures. The highest Y value at 0.1 mol fraction EtOH is probably caused by the reagent solvation changes at the initial additions of EtOH to water. Extremes in the thermodynamic parameters of reagent solvation and complex formation reactions at high concentrations of water in H_2O–EtOH solvents have been observed previously [30]. Such effects could be explained by strengthening of the three-dimensional spatial network as water hydrogen bonds occur at the first addition of an organic solution to the solvent [31].

Solid-state studies

The results of Fourier transform infrared spectroscopy analysis

In the IR spectrum of BA (Fig. 2), the valence vibrations of the N–H bonds in the primary amino group and the C–H bonds in the aromatic ring with maxima at 3424 cm^{-1} and 3068, 2836, 2681, 2558 cm^{-1}, respectively, are registered.

The absorption bands with maxima at 1605, 1581 and 1495 cm^{-1} belong to the valence vibrations of the C=C bonds in the benzene ring. The band of valence vibrations of the C=O bond in the carboxyl group (COOH) is observed at 1682 cm^{-1}. The valence vibrations of the C–N bond in the amino group connected with benzene ring are observed at 1321 cm^{-1}. The bands of the deformation vibrations of the N–H bonds in the amino group and the C-H bonds in the benzene ring are registered at 927 cm^{-1} and 1178, 1124, 808 cm^{-1}, respectively [32].

In the FTIR spectrum of βCD, the wide band is registered with the absorption at 3407 cm^{-1}, which is caused by the valence vibrations of the O–H bonds in the primary hydroxyl groups [33]. Also, the absorption band with maximum at 2925 cm^{-1} is observed. It belongs to the valence vibrations of the C–H bonds in the CH- and CH_2-groups. Absorption maxima at 1641 cm^{-1} and 1417, 1365, 1246, 1158 cm^{-1} belong to the deformation vibrations of the O–H in the COH and C-H in the CH_2OH, CHOH groups, respectively. In the interval of 1200–1030 cm^{-1}, the absorption bands of the valence vibrations of the C-O bonds in the ether and hydroxyl groups of βCD (1081 and 1029 cm^{-1}) are registered. The absorption bands in the region 950–700 cm^{-1} (940, 857, 754 and 709 cm^{-1}) belong to the deformation vibrations of the C–H bonds and the pulsation vibrations in glucopyranose cycle. The main differences in the spectra of BA and inclusion complex were observed in the frequency range from 2500 to 3100 cm^{-1}, corresponding to aromatic hydrogen vibrations [34]. These vibrations are highly attenuated in mixtures, which is probably due to the inclusion of the acid aromatic rings in the cavity. The band of the valence vibrations of the C=O bond in the carboxyl group of BA is shifted to higher wave number in the spectral pattern of the inclusion complex and registered at 1699 cm^{-1}. The absorption bands of the valence vibrations of the C–O bonds in the ether and hydroxyl groups of βCD in the interval of 1200–1030 cm^{-1} are slightly broadened for the inclusion complex. Moreover, the absorption bands of the valence vibrations of the C=C bonds in the benzene ring are shifted to 1650, 1599 and 1583 cm^{-1}. The peak at 1246 cm^{-1} in the spectrum of βCD which belongs to the deformation vibrations of

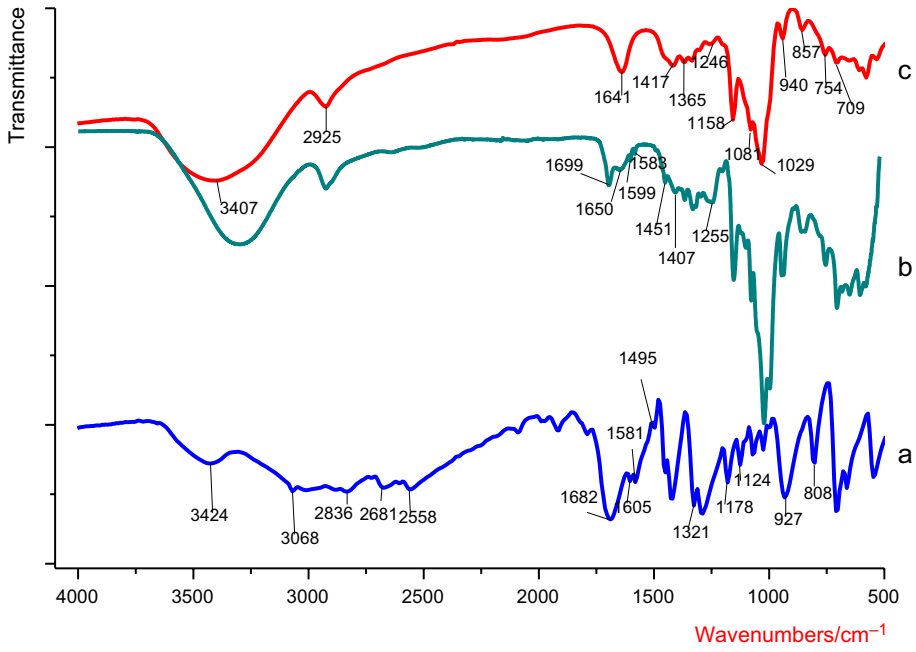

Fig. 2 FTIR spectra of raw BA (**a**), complex BA-*β*CD (**b**) and βCD (**c**)

the C–H bonds in the hydroxyl groups is shifted to the 1255 cm^{-1} and greatly broadened.

The results of DSC analysis

The experiments have been carried out on the BA, βCD, as well as on the inclusion complex. The peak temperature is the temperature at the maximum of the thermal event. This temperature is highly dependent on the sample crystallinity, crystal size, sample preparation and heating rate, which makes this value unreliable for comparison. On the contrary, the onset temperature remains unchanged. The melting temperature, T_{onset}, is defined by the extrapolated beginning of the curve, being determined by the point of intersection of the tangent with the point of maximum slope, on the principal side of the peak with the extrapolated baseline.

Figure 3 shows that the BA sample presents onset temperatures for melting and boiling of 118 °C and 242 °C, respectively. Literature values for this transition are 115.4 °C [35]; 121.4 °C [36] and 122.35 °C [37]. Thus, the data deviate by 2.6÷4.35 °C from the available literature data. Possible reasons for the discrepancies may be related to the differences in the purity levels of compounds analyzed or to the accuracy of the method used to determine literature values.

In the case of βCD, the endothermic peak with the onset temperature of 84 °C was revealed (Fig. 3, curve c). At this temperature, endothermic effect belongs to the release of water molecules from the inner cavity of βCD. Curve b displays the DSC trace of complex BA-*β*CD. The endothermic peak (T_{onset} = 45 °C) is related to the water loss and more importantly, therefore, indicates the presence of a fraction of βCD, which does not interact with the guest molecule. The complete disappearance of the BA endothermic peak was observed for complex instead. This phenomenon can be assumed as proof of interactions between the components of the respective binary systems [38]. This can be considered as indicative of BA amorphization and inclusion complex formation.

Solubility studies: phase solubility diagram

The calibration equation of BA in water was set up to build phase solubility diagram by UV–Vis spectroscopies. Calibration equation of BA in water is $y = -0.01877 + 835.6 \times$ with $R^2 = 0.998$, where y is optical densities and x is concentration of BA in the solution. This equation was used for calculating BA concentration in the solution containing βCD. Results indicated that in water, BA concentration increases linearly with increasing βCD (Fig. 4). The slope of the line is 0.0367 with $R^2 = 0.995$. The linear profile of the diagram points at a 1:1 stoichiometric ratio as for the formation of BA-*β*CD complex.

Stability constant of the complex connects the concentration of the complexes formed with the concentrations of the reagents in Eq. (3) and was found to be $\lg K = 1.99$ that falls within the literature values (lgK = 1.94 [1], $\lg K = 2.6$ [2]).

Thermodynamics of complex formation in water–ethanol solvents

The thermodynamic parameters ($\lg K$, $\Delta_r H$, $\Delta_r G$, $T\Delta_r S$) of complex formation have been calculated by the program HEAT [39]. The analysis of the experimental data treatments by HEAT was reported earlier in detail [22–24]. The

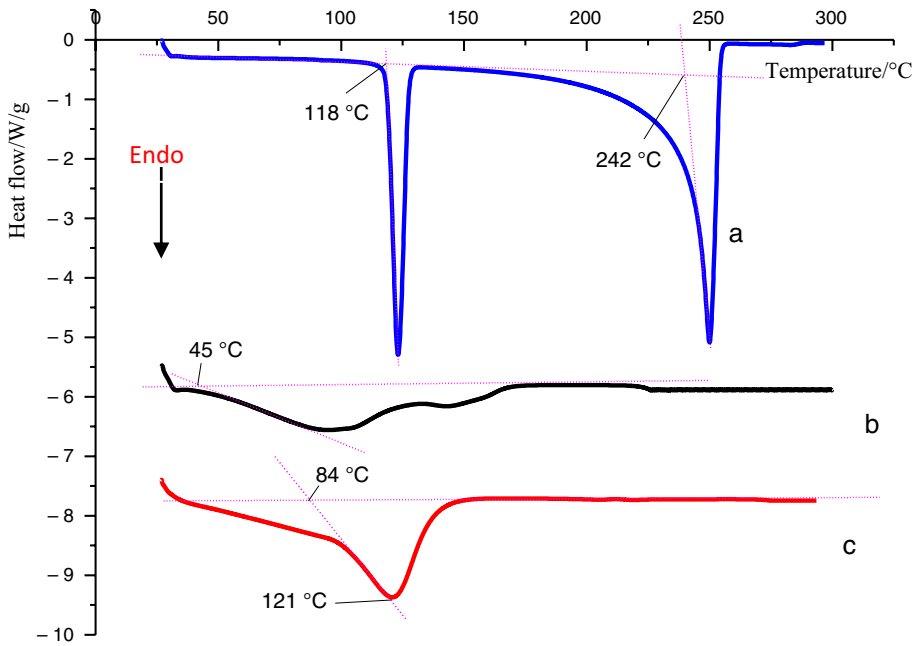

Fig. 3 DSC curves of BA (**a**), inclusion complex BA-*β*CD (**b**) and βCD (**c**)

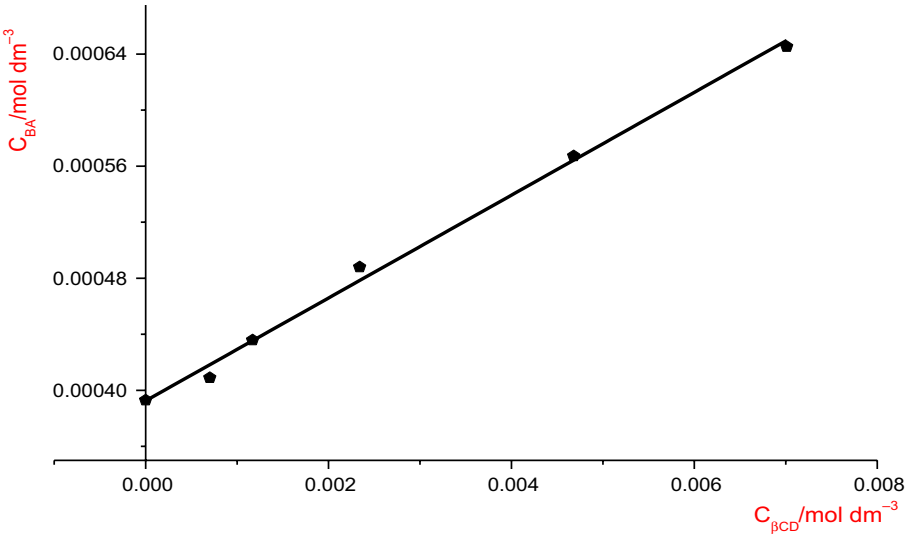

Fig. 4 Phase solubility diagram for the binary complex BA-βCD in water

thermodynamic parameters of reaction (1) in H_2O–EtOH solvents are presented in Table 3.

The thermodynamic parameters of BA-βCD complex formation in water were determined using a calorimetric method and were in agreement with the data in [2, 17, 40]. The absence of any information about the activity coefficients of reagents leads to the evaluation of association parameters which are not exactly defined thermodynamically. Only an apparent constant can be determined, and consequently, the standard Gibbs energy, enthalpy and entropy suffer from the same limitations.

The increase in EtOH concentrations in the mixed solvent leads to the decrease in the stability of BA-βCD complex and enhancement in the exothermicity of its formation reaction.

An increase in the exothermicity of complexation is accompanied by a decrease in the entropic contribution to the change in the Gibbs energy.

The thermodynamics of a complex formation (1) was discussed by the analysis of the reagent solvation contributions to thermodynamic parameters of the reaction on the basis of the solvation-thermodynamic approach [42]. According to the solvation-thermodynamic approach, the influence of the change in solvent composition on the reaction (1) ($\Delta_r Y_{(solvent)}$, $\Delta_r Y_{(water)}$) and on the thermodynamic parameters of solvation of each reagent and product ($Y(Z)_{(solvent)}$, $Y(Z)_{(water)}$) can be quantitatively described by the following equations:

$$\Delta_{tr} Y_r = \Delta_r Y_{(solvent)} - \Delta_r Y_{(water)} \quad (4)$$

$$\Delta_{tr} Y(Z) = Y(Z)_{(solvent)} - Y(Z)_{(water)} \quad (5)$$

where $\Delta_{tr} Y_r$ and $\Delta_{tr} Y(Z)$ are the thermodynamic function ($\Delta_{tr} H$, $\Delta_{tr} G$, $T\Delta_{tr} S$) of transfer for the reaction and the reagents, respectively.

Table 3 Thermodynamic parameters of BA-βCD complex formation reaction (lg$K$, $\Delta_r H$, $\Delta_r G$, $T\Delta_r S$) with different mole fractions of ethanol in the binary H_2O–EtOH solvent (X_{EtOH}) and solution pH at T = 298.15 K

X_{EtOH} molar fraction	lg$K$	$-\Delta_r H$/kJ mol^{-1}	$-\Delta_r G$/kJ mol^{-1}	$-T\Delta_r S$/kJ mol^{-1}	Method and pH
0.00	2.4 ± 0.1	12.2 ± 0.5	13.7 ± 0.6	− 1.5 ± 0.8	Calorimetry, pH = 3.6
	1.99	–	11.4	–	Higuchi-Connors
	1.94		11.3		Higuchi-Connors, pH = 2.9 [1]
	2.6 ± 0.1	13.4 ± 0.4	14.7	− 1.3	Calorimetry, acid medium [17]
	2.5	22.3 ± 0.3	14.4	7.9	Circular dichroism [40]
	2.5	–	14.2	–	^{1}H NMR, acid medium [2]
	2.1	32 ± 11	12	20	Calorimetry [41]
	2.4	–	13.7	–	Densitometry, acid medium [2]
0.10	1.9 ± 0.1	36.8 ± 0.2	10.8 ± 0.6	26.0 ± 0.7	Calorimetry, pH = 3.6
0.20	0.7 ± 0.1	44.3 ± 0.6	3.9 ± 0.6	40.4 ± 0.8	Calorimetry, pH = 3.6

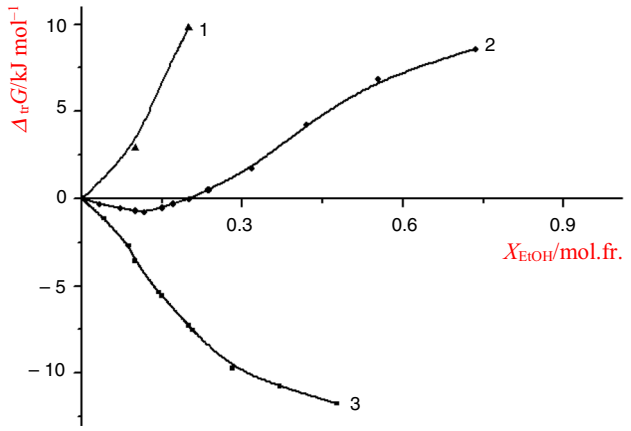

Fig. 5 Influence of water–ethanol solvent on the Gibbs energy changes in the transfer of the complex formation reaction (1) and solvation of reagents from H_2O to H_2O–EtOH. 1-$\Delta_{tr}G_r$; 2-$\Delta_{tr}G$(βCD) [26]; 3-$\Delta_{tr}G$(BA) [29]

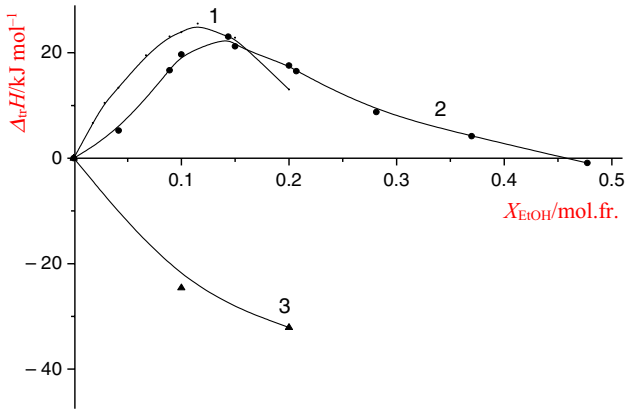

Fig. 6 Influence of water–ethanol solvent on the enthalpy changes in the transfer of the complex formation reaction (1) and solvation of reagents from H_2O to H_2O–EtOH. 1-$\Delta_{tr}H$(βCD) [43]; 2-$\Delta_{tr}H$(BA) [29]; 3-$\Delta_{tr}H_r$

The transfer thermodynamic functions of Gibbs energy ($\Delta_{tr}G_r$) for reactions (1) were calculated as follows:

$$\begin{aligned}\Delta_{tr}G_r &= \Delta_rG_{(r,s)} - \Delta_rG_{(r,w)} \\ &= -2.303RT(\lg K(\text{BA-}\beta\text{CD})_s \\ &\quad - \lg K(\text{BA-}\beta\text{CD})_w \end{aligned} \quad (6)$$

where $\lg K(\text{BA-}\beta\text{CD})_s$ and $\lg K(\text{BA-}\beta\text{CD})_w$ are stability constants of BA-*β*CD complex in water–ethanol solvents and in water, respectively, which are presented in Table 3.

The influence of the composition of H_2O–EtOH solvents on the change in Gibbs energy of reactions (1) and desolvation of reagents is shown in Fig. 5.

The values $\Delta_{tr}G$(βCD) are nearly zero at the X(EtOH) = 0.0 ÷ 0.2 mol fraction concentration. Thus, the decrease in the stability of the complex is determined by solvation of BA ($\Delta_{tr}G$(BA)) and desolvation of complex.

When adding a small EtOH amount to the solvent ($X_{EtOH} < 0.05$ mol fraction), the increase in exothermicity of complex formation reaction ($\Delta_{tr}H_r$) is determined by desolvation of βCD (Fig. 6).

Conclusions

Previously, we found that solvents H_2O–EtOH, H_2O-DMSO and H_2O-Me_2CO have similar effect on the thermodynamic parameters of formation of the host–guest complex formations between macrocyclic molecules 18-crown-6 (18C6) and glycyl–glycyl–glycine, glycine, D,L-alanine and L-phenylalanine [22, 25, 44]. These molecular complexes became more stable when adding the organic component to the solvent. In contrast, the increase in EtOH concentration led to the decrease in the BA-*β*CD complex stability, as in the case of the complex formation of hydroxypropyl-β-cyclodextrin with quercetin [45]. Changes in the Gibbs energy of molecular complexes formed by the "host" molecules 18C6 and βCD, however, are due to the resolvation of "guest" molecules. In cases of complexes with 18C6, the desolvation of "guests" is observed, and in the BA-*β*CD complexes, the increase in BA solvation occurs.

Furthermore, an increase in exothermicity of both types of complex formation reactions in H_2O–EtOH mixed solvents is observed. An increase in the concentration of ethanol leads to an increase in the entropy contribution of BA-*β*CD complex formation reaction, which decreases the stability of BA-*β*CD.

In conclusion, addition of small amounts of ethanol to water has put impact on the complex formation and therefore thermodynamic studies are important for improving bioavailability of "guest" in nonaqueous media.

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